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| ART UNIT | PAPER NUMBER |
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| 1636 | |

DATE MAILED: 08/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/693,905 | LAHTINEN ET AL. | |
| | Examiner | Art Unit | |
| | Jennifer Dunston | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 December 2005 and 10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *50-68,70-76 and 78-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-68,70-76 and 78-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This action is in response to the amendments, filed 12/27/2005 and 4/10/2006, in which claims 69 and 77 were canceled, and claims 68, 76, 78, 82, 90, 93, 98, 101, 106, 109, 114, 117, 122 and 125 were amended. Currently, claims 50-68, 70-76 and 78-129 are pending and under consideration.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 8/25/2005. Therefore, this action is not final.

### *Priority*

An applicant in a nonprovisional application may claim the benefit of the filing date of one or more prior foreign applications under the conditions specified in 35 U.S.C. 119(a) through (d) and (f), 172, and 365(a) and (b). In an original application filed under 35 U.S.C. 111(a), the claim for priority must be presented during the pendency of the application, and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. This time period is not extendable. The claim must identify the foreign application for which priority is claimed, as well as any foreign application for the same subject matter and having a filing date before that of the application for which priority is claimed, by specifying the application number, country (or intellectual property authority), day, month, and year of its filing.

The instant application was filed under 35 U.S.C. 111(a). Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) or 365(a) based upon an application filed in Finland on 4/30/2001 and an international application filed in Sweden on 4/30/2002. A claim for priority under 35 U.S.C. 119(a)-(d) or 365(a) cannot be based on said applications, since the United States application was filed more than twelve months thereafter.The effective filing date of claims 50-68, 70-76 and 78-129 is 10/28/2003.

### *Oath/Declaration*

The oath or declaration filed 11/25/2005 is accepted.

### *Claim Objections*

Claims 55, 63, 71, 79, 87, 95, 111 and 119 are objected to because of the following informalities: the term "claim" should be used in place of the term "claims" in reference to the preceding claim to improve the grammar. Appropriate correction is required. This is a new objection.

Claims 93, 101, 109, 117 and 125 are objected to because of the following informalities: the term "lentivirus" is misspelled. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66, 67, 70-73 and 82-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection has been altered to address the amendments to the claims in the reply filed 4/10/2006.

Claim 66 is vague and indefinite in that the metes and bounds of the phrase "composition comprising an extracellular superoxide dismutase" are unclear. It is unclear if the extracellular superoxide dismutase is a protein or a nucleic acid molecule encoding an extracellular superoxide dismutase protein. The dependent claims refer back to "the nucleic acid" of claim 66; however, it is unclear if the composition comprises a nucleic acid. If the claim is amended to recite "a nucleic acid encoding extracellular superoxide dismutase," claims 66-73 would be objected to as being duplicates of claims 50-57.

Claims 67 and 70-73 depend from claim 66 and are indefinite for the same reasons as applied to claim 66.

Claim 70 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 70 depends from claim 66, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 66 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 82 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. The nucleic acid would have to code for an

extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase. For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 83-89 depend from claim 82 and are indefinite for the same reasons as applied to claim 82.

Claim 90 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product that of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. The nucleic acid would have to code for an extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase. For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 91-97 depend from claim 90 and are indefinite for the same reasons as applied to claim 90.

Claim 98 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. The nucleic acid would have to code for an extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase.

For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 99-105 depend from claim 98 and are indefinite for the same reasons as applied to claim 98.

Claim 106 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. The nucleic acid would have to code for an extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase. For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 107-113 depend from claim 106 and are indefinite for the same reasons as applied to claim 106.

Claim 114 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. The nucleic acid would have to code for an extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase. For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 115-121 depend from claim 114 and are indefinite for the same reasons as applied to claim 114.

Claim 122 is vague and indefinite in that the metes and bounds of the phrase "wherein the nucleic acid encodes a translation or transcription product of extracellular superoxide dismutase protein" are unclear. It is unclear if the nucleic acid encodes extracellular superoxide dismutase or whether it encodes a protein whose transcript or protein levels are altered directly or indirectly by an extracellular superoxide dismutase protein. If the nucleic acid encodes extracellular superoxide dismutase, it is unclear how a transcript or protein level could be encoded by the nucleic acid. The nucleic acid would have to code for an extracellular superoxide dismutase transcript that encodes the extracellular superoxide dismutase. For the purposes of examination, the phrase has been interpreted as limiting the nucleic acid to a nucleic acid encoding extracellular superoxide dismutase.

Claims 123-129 depend from claim 122 and are indefinite for the same reasons as applied to claim 122.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-68, 70-76 and 78-129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection has been rewritten since the Office action mailed 8/25/2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid encoding an extracellular superoxide dismutase or an extracellular superoxide dismutase protein. The amount of the nucleic acid administered must be sufficient to treat and/or prevent restenosis, treat and/or prevent blood vessel thickening, decrease macrophage accumulation, increase endothelial cell growth, or inhibit hyperplastic connective tissue growth.

The nature of the subject matter is complex, because the nucleic acid or protein must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

*Breadth of the claims:* The claims are broad in that they encompass local or systemic delivery of the nucleic acid or protein to any species of organism. With respect to nucleic acid delivery, the claims are broad in that any vector may be used to deliver the nucleic acid encoding an extracellular superoxide dismutase.

*Predictability and state of the art:* An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al

(Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

French et al (US Patent No. 6,290,949) teach that the concept of direct gene transfer to inhibit restenosis was first articulated in the context of retrovirus- and lipofectin-mediated gene transfer; however, the absolute level of recombinant protein produced *in vivo* by these techniques was to low to be considered therapeutically significant (e.g. column 10, lines 43-50). Further, French et al teach that ventricular myocytes do not divide, and thus retroviral vectors cannot be employed to deliver therapeutic nucleic acid molecules to the cardiac muscle cells (e.g. column 12, lines 48-63). Further, Kotani et al (Current Gene Therapy, Vol. 4, No. 2, pages 183-194, 2004) teach that naked plasmid DNA is generally unstable because it is taken up by endocytosis and is rapidly degraded in the lysosome (e.g. page 183, paragraph bridging columns).

With regard to Sendai virus vectors, Kotani et al teach that the envelope hemagglutinating virus or Japan (HVJ or Sendai virus) rather than the viral genome is a

promising gene therapy vector with low toxicity and immunogenicity (e.g. page 188, right column; Table 2). However, there is no precedent case of clinical applications (Kotani, 2004; e.g. paragraph bridging pages 191-192). Systemic safety and toxicology studies are required for the clinical use of HVJ envelope vectors (Kotani, 2004; e.g. paragraph bridging pages 191-192).

The prior art also taught that successful treatment of restenosis in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. Vol. 19, No. 2, pages 418-432, 1992) taught that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of a therapeutic result in a rabbit model by delivery of an adenoviral vector comprising a nucleic acid sequence encoding superoxide dismuatase to the precise site of vascular damage (e.g. specification, pages 63-67). With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life (e.g. page 420, paragraph bridging columns 1-

2). Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies (e.g. Abstract).

Lafont et al (Ann. Card. Ang. Vol. 44, No. 7, pages 349-353, 1995), reviewed the results of fifteen years of research prior to 1995, and concluded that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract.

Lafont et al (Card. Res. Vol. 39, No. 1, pages 50-59, 1998) indicated that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. The same concerns would apply to the treatment of stenosis, due to the differences in physiology among the various models.

Stephan et al (Fundam. Clin. Pharmacol. Vol. 11, pages 97-110, 1997) confirmed the unpredictable state of the art of animal models of restenosis stating, "there are significant differences between the models and their fidelity to human vascular lesions. Three animal species, the rat, the rabbit, and the pig, are commonly used in restenosis studies. Results among these species have been shown to differ significantly, raising issues of suitability of animal models for restenosis." See page 103, first full paragraph of column 2. With respect to the

rabbit model, Stephan taught that drugs developed using this model failed to demonstrate the same effect in human coronary restenosis. See page 104, column 1, lines 20-22.

Johnson et al (Thromb. Haemost. Vol. 81, pages 835-843, 1999) taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions (e.g. Abstract).

The post-filing art shows that extrapolation of results of small animal restenosis remains unpredictable. Appleby and Kingston (Current Gene Therapy, Vol. 4, pages 153-182, 2004) indicated that despite promising results from numerous animal studies, there has been a general failure to obtain similar results in humans. This is primarily due to an incomplete understanding of the vascular biology of restenosis which makes it difficult to select therapeutic genes, dissimilarity between humans and the animal models under study, and difficulty in obtaining localized gene transfer into coronary arteries in vivo. The authors concluded that progress in each area will be required before gene therapy in the vasculature becomes a clinical reality. See abstract and last two paragraphs on page 176.

With regard to xenografts in the treatment of cardiac disease, Platt (J Card Surg, Vol. 16, pages 439-447, 2001) teaches that the main hurdle to clinical application is the immune response of the recipient against the graft (e.g. Abstract). Xenografts may be subject to primary non-function, failure of neovascularization, failure of the microenvironment to support the tissue, acute vascular rejection or hyperacute rejection (e.g. Figure 1).

As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes

resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Furthermore, at the time of the invention, those of skill in the art recognized that one could not predictably extrapolate positive results from small animal models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to provide guidance that would allow such extrapolation, and the post-filing art provides objective evidence that a substantial portion of the claimed scope of the invention is non-functional.

*Guidance of the specification and existence of working examples:* The specification teaches that trauma to the blood vessel endothelium results in the formation of excessive connective tissue and inflammatory reaction and subsequent occlusion because of thrombosis or restenosis (e.g. page 4, lines 1-3; paragraph bridging pages 10-11). To address these physiologic response to trauma, the specification broadly envisions the administration of a nucleic acid encoding an extracellular superoxide dismutase (EC-SOD), EC-SOD protein, a protein that results in increased EC-SOD or a nucleic acid encoding a protein that results in increased EC-SOD (e.g. paragraph bridging pages 11-12). The specification envisions the local or systemic administration of the nucleic acid encoding EC-SOD in the form of naked nucleic acid, in a viral vector such as a retrovirus, Sendai virus, lentivirus, adeno-associated virus or adenovirus, in a liposome, or in an artificial chromosome (e.g. page 13, lines 5-20; pages 22-23; pages 27-28).

The specification does not teach how to make and use any nucleic acid encoding any protein that is capable of increasing the expression of endogenous EC-SOD. The only nucleic acid sequence taught by the specification that is capable of increasing EC-SOD protein is the EC-SOD nucleic acid sequence (e.g. paragraph bridging pages 32-33). The specification does not overcome the limitations of the use of naked DNA or viral vectors such as retroviruses, Sendai virus or adeno-associated virus to achieve therapeutic expression of EC-SOD. Further, the specification states the following with regard to retroviral vectors:

> Retroviruses have several drawbacks *in vivo* which limit their usefulness. They provide stable gene transfer, but current retroviruses are unable to transduce replicating cells. The potential hazards of transgene incorporation into the host DNA are not warranted if short-term gene transfer is sufficient. See page 22, lines 25-29.

The specification does not provide any working examples that demonstrate the systemic safety of any Sendai virus vector.

The claims read on the administration of a composition comprising cell containing a nucleic acid encoding EC-SOD (i.e. *ex vivo* gene therapy). The instant specification recognized *ex vivo* gene delivery as a method to deliver a therapeutic nucleic acid (e.g. paragraph bridging pages 21-22). The specification contemplates the administration of xenografts, allografts or autografts as tissue sources for gene therapy compositions (e.g. paragraph bridging pages 58-59). The specification does not teach the expression of EC-SOD in xenogeneic tissues sufficient to overcome the immune system mediated rejection of xenogeneic tissues. Further, the specification does not disclose any working examples that teach the administration of cells, either xenogeneic, allogenic or autogenic, that express EC-SOD and are capable of treating and/or preventing restenosis, treating and/or preventing blood vessel thickening, decreasing

macrophage accumulation, increasing endothelial cell growth, or inhibiting hyperplastic connective tissue growth.

The working example discloses the administration to a rabbit stenosis model an adenoviral vector comprising a rabbit lung cDNA encoding EC-SOD (e.g. pages 63-65). Adenoviral vector ($3x10^9$ pfu/kg) was administered three days after the denudation of aortic endothelium (e.g. page 65, lines 3-13). The administration of the adenoviral vector encoding EC-SOD resulted in a significant reduction in neointima formation with a reduction in macrophage infiltration (e.g. page 66, lines 11-23; page 67, lines 11-27). Further, the EC-SOD treated group had significantly more endothelial recovery (e.g. paragraph bridging pages 66-67).

*Amount of experimentation necessary:* The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods. The successful outcome observed in the rabbit model treated with the adenoviral vector encoding an EC-SOD protein is not necessarily predictive of the outcome when other vectors are used in rabbit and cannot be extrapolated to any other species, especially larger mammals. With any EC-SOD nucleic acid or protein, one would have to determine how to deliver the composition to the appropriate target cells with specificity and efficiency, sufficient to induce the claimed therapeutic effects. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so. The nature of the experimentation is not routine.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an

undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 50-68, 70-76 and 78-129 are not considered to be enabled by the instant specification.

Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claim is drawn to the administration of an EC-SOD protein in a liposome. The instant specification envisions the administration of nucleic acid molecules in a liposome, but does not envision the administration of EC-SOD protein in a liposome. The specific portions of the specification pointed to in the reply filed 4/10/2006 fail to provide support for claim 78, and a thorough review of the specification did not reveal any portions that provide literal or inherent support for the claimed embodiment.

Accordingly, the amendment is a departure form the specification and claims as originally filed.

***Response to Arguments - 35 USC § 112***

The previous rejection of claims 68, 69 and 74-81 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims.

With respect to the rejection of claims 66, 67 and 70-73 under 35 U.S.C. 112, second paragraph, Applicant's arguments filed 12/27/2005 have been fully considered but they are not

persuasive. The response asserts that the claims have been amended to recite the term "protein" whenever necessary to overcome the rejection. However, claim 70 recites "the nucleic acid" in reference to claim 66. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claim 50-129 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicant's arguments filed 4/10/2006 have been fully considered but they are not persuasive.

The response asserts that recitation of Sendai viruses have been removed. This is not found persuasive, because claims 53, 61, 85 and 93 refer to the use of Sendai virus.

With respect to other viral vectors, including AAV, MLV, the response asserts that they have a structure similar to adenovirus and have been shown to be capable of infecting vascular wall cells. Given the art recognized problems with obtaining a sufficient amount of gene expression, it is not clear that AAV and MLV vectors will provide sufficient expression to induce any therapeutic effect. French et al (US Patent No. 6,290,949) teach that the concept of direct gene transfer to inhibit restenosis was first articulated in the context of retrovirus- and lipofectin-mediated gene transfer; however, the absolute level of recombinant protein produced *in vivo* by these techniques was to low to be considered therapeutically significant (e.g. column 10, lines 43-50). Further, the response asserts that because the proliferation of vascular wall cells is limited, it is highly unlikely that retro/lentivirus integration to vascular smooth muscle cell genome would cause transformation of cells to carcinogenic cells. While the vascular smooth muscle cells have low rates of proliferation, and thus may be less susceptible to neoplastic

transformation, other cells will be exposed to the retrovirus. The claims are drawn to both local and systemic administration of the therapeutic nucleic acid. Thus, rapidly dividing cells will be exposed to the retrovirus. Furthermore, the instant specification teaches that EC-SOD expression showed a similar pattern of tissue distribution as LacZ staining, which was present in the spleen, lung and liver even after local gene delivery (e.g. page 64, lines 22-31). See also Laukkanen et al (Circulation, Vol. 106, pages 1999-2003, September 16, 2002) at pages 2000-2001 (Expression of LacZ and EC-SOD).

The response asserts that the claims do not read on the administration of a composition comprising a cell containing a nucleic acid encoding EC-SOD. This is not found persuasive, because the method is not limited to the administration of a virus or naked nucleic acid isolated from a cell. The instant specification recognized *ex vivo* gene delivery as a method to deliver a therapeutic nucleic acid (e.g. paragraph bridging pages 21-22), and a cell containing the nucleic acid encoding EC-SOD is a composition comprising the nucleic acid to be delivered. Further, the instant specification envisions administering nucleic acid molecules encoding EC-SOD in compositions comprising cells (e.g. paragraph bridging pages 58-59).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 82-129 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Applicant's arguments with respect to claims 82-129 have been considered but are moot in view of the new ground(s) of rejection under 35 U.S.C. 112, second paragraph.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 50, 51, 53, 58, 59, 61, 82, 83, 85, 90, 91, 93, 98, 99, 101, 106, 107, 109, 114, 115, 117, 122, 123 and 125 are rejected under 35 U.S.C. 102(b) as being anticipated by Laukkanen et al (Circulation, Vol. 106, pages 1999-2003, September 16, 2002; see the entire reference). This is a new rejection.

Regarding claim 50, the instant specification defines the term "restenosis" as growth of connective tissue after performing a dilating procedure with or without an implant leading to connective tissue growth in the tubular structure with following narrowing of the tubular structure" (page 15, lines 21-23). Laukkanen et al teach the balloon denudation of the abdominal aorta of a rabbit, which, in the absence of treatment, results in narrowing of the tubular structure due to the growth of connective tissue (e.g. page 2000, Animal Experiments; pages 2001-2002, Histological Analysis; Figures 2 and 3). Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid encoding EC-SOD in an amount sufficient to reduce the narrowing of the aorta (reduce restenosis) (e.g. pages 2001-2002, Histological Analysis; Figures 2 and 3).

Regarding claim 51, Laukkanen et al teach a reduction in restenosis when the adenovirus composition is delivered locally (e.g. pages 2001-2002, Histological Analysis; Figures 2 and 3).

Regarding claim 53, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claim 58, Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid sequence encoding EC-SOD to a rabbit in an amount sufficient to reduce blood vessel thickening (e.g. page 2000, left column; page 2001, paragraph bridging columns).

Regarding claim 59, Laukkanen et al teach a reduction in blood vessel thickening when the adenovirus composition is delivered locally (e.g. page 2001, paragraph bridging columns; paragraph bridging pages 2002-2003).

Regarding claim 61, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claim 82, the instant specification defines the term "restenosis" as growth of connective tissue after performing a dilating procedure with or without an implant leading to connective tissue growth in the tubular structure with following narrowing of the tubular structure" (page 15, lines 21-23). Laukkanen et al teach the balloon denudation of the abdominal aorta of a rabbit, which, in the absence of treatment, results in narrowing of the tubular structure due to the growth of connective tissue (e.g. page 2000, Animal Experiments; pages 2001-2002, Histological Analysis; Figures 2 and 3). Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid encoding EC-SOD in an amount sufficient to reduce the narrowing of the aorta (reduce restenosis) (e.g. pages 2001-2002, Histological Analysis;

Figures 2 and 3). The adenoviral vector was provided in a biologically compatible medium as a clinical-grade adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claim 83, Laukkanen et al teach a reduction in restenosis when the adenovirus composition is delivered locally (e.g. pages 2001-2002, Histological Analysis; Figures 2 and 3).

Regarding claim 85, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claim 90, Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid sequence encoding EC-SOD to a rabbit in an amount sufficient to reduce blood vessel thickening (e.g. page 2000, left column; page 2001, paragraph bridging columns). The adenoviral vector was provided in a biologically compatible medium as a clinical-grade adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claim 91, Laukkanen et al teach a reduction in blood vessel thickening when the adenovirus composition is delivered locally (e.g. page 2001, paragraph bridging columns; paragraph bridging pages 2002-2003).

Regarding claim 93, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus production).

Regarding claim 98, Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid encoding EC-SOD to a rabbit in an amount sufficient to decrease macrophage accumulation (e.g. page 2000, left column; Figures 2 and 3).

Regarding claim 99, Laukkanen et al teach a decrease in macrophage accumulation when the adenovirus composition is delivered locally (e.g. page 2001, paragraph bridging columns; paragraph bridging pages 2002-2003; Figures 2 and 3).

Regarding claim 101, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus production).

Regarding claims 106, 114 and 122, Laukkanen et al teach the administration of an adenoviral vector comprising a nucleic acid sequence encoding EC-SOD to a rabbit in an amount sufficient to increase endothelial cell growth (e.g. page 2000, left column; page 2002, left column, first paragraph; Figure 2). The adenoviral vector was provided in a biologically compatible medium as a clinical-grade adenovirus (e.g. page 2000, Adenovirus Production).

Regarding claims 107, 115 and 123, Laukkanen et al teach an increase in endothelial cell growth when the adenovirus composition is delivered locally (e.g. Figures 2 and 3).

Regarding claims 109, 117 and 125, the viral vector used by Laukkanen et al is an adenovirus (e.g. page 2000, Adenovirus production).

Claims 50, 51, 53, 57-59, 61, 65-68, 71, 73-76, 79, 81-83, 85, 87, 89-91, 93, 95, 97-99, 101, 103, 105-107, 109, 11, 113-115, 117, 119, 121-123, 125, 127 and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by March (US Patent No. 5,552,309; see the entire reference), as evidenced by Marklund et al (US Patent No. 5,366,729, of record). This is a new rejection.

Regarding claim 50, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the

adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63).

Regarding claim 51, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claim 53, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claim 57, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Regarding claim 58, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). March teaches the administration of up to $10^{14}$ pfu (e.g. column 6, lines 40-60). Absent any evidence to the contrary, this amount would be sufficient to treat blood vessel thickening.

Regarding claim 59, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claim 61, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claim 65, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Regarding claims 66 and 74, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). The cells administered by March will comprise extracellular superoxide dismutase protein. Marklund et al is cited only to show that the EC-SOD protein secreted by the cells in culture exists in equilibrium between the medium (plasma phase) and the glycocalyx of the vessel endothelium (e.g. column 2, lines 10-17). The treatment of restenosis will necessarily result in a reduced blood vessel thickening.

Regarding claims 67 and 75, March teaches the local delivery of the cells comprising EC-SOD protein (e.g. column 6, lines 23-39).

Regarding claims 68, 71, 76 and 79, March teaches the delivery of vascular cells such that they remain viable and thus are in a biologically compatible medium (e.g. column 6, lines 23-39). The EC-SOD protein in the biologically compatible medium will comprise biomolecules of the cell being transferred.

Regarding claims 73 and 81, March teaches the treatment of a human (e.g. column 6, lines 55-56).

Regarding claim 82, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). March teaches the administration of up to $10^{14}$ pfu (e.g. column 6, lines 40-60). March teaches the use of a physiologically acceptable (i.e. biologically compatible) medium to deliver the adenovirus (e.g. paragraph bridging columns 6-7).

Regarding claim 83, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claim 85, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claim 87, the polyol and buffers taught by March are biomolecules. Further, March teaches the delivery of the adenovirus in a gel or matrix (e.g. column 9, lines 32-51).

Regarding claim 89, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Regarding claim 90, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). March teaches the administration of up to $10^{14}$ pfu (e.g. column 6, lines 40-60). March teaches the use of a physiologically acceptable (i.e. biologically compatible) medium to deliver the adenovirus (e.g. paragraph bridging columns 6-7).

Regarding claim 91, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claim 93, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claim 95, the polyol and buffers taught by March are biomolecules. Further, March teaches the delivery of the adenovirus in a gel or matrix (e.g. column 9, lines 32-51).

Regarding claim 97, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Regarding claim 98, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). March teaches the administration of up to $10^{14}$ pfu (e.g. column 6, lines 40-60). March teaches the use of a physiologically acceptable (i.e. biologically compatible) medium to deliver the adenovirus (e.g. paragraph bridging columns 6-7). Absent any evidence to the contrary, the dose taught by March would be sufficient to decrease macrophage accumulation.

Regarding claim 99, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claim 101, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claim 103, the polyol and buffers taught by March are biomolecules. Further, March teaches the delivery of the adenovirus in a gel or matrix (e.g. column 9, lines 32-51).

Regarding claim 105, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Regarding claims 106, 114 and 122, March teaches the administration of adenoviral vector particles which include at least one nucleic acid sequence encoding a therapeutic agent for treating a disease of the blood vessel wall, such as restenosis, in combination with a polyol, to vascular cells *in vitro* (e.g. column 6, lines 23-39). The vascular cells are then re-implanted into the vascular wall, whereby such re-implanted cells express the agent for treating the blood vessel wall *in vivo* (e.g. column 6, lines 23-39). Further, March teaches the administration of the adenoviral particles in combination with the polyol *in vivo* (e.g. column 6, lines 40-60). March teaches the use of extracellular superoxide dismutase (EC-SOD) as a DNA sequence encoding a therapeutic agent for use in the abovementioned method (e.g. column 7, lines 6-63). March teaches the administration of up to $10^{14}$ pfu (e.g. column 6, lines 40-60). March teaches the use of a physiologically acceptable (i.e. biologically compatible) medium to deliver the adenovirus (e.g. paragraph bridging columns 6-7). Absent any evidence to the contrary, the dose taught by March would be sufficient to increase endothelial cell growth.

Regarding claims 107, 115 and 123, March teaches the administration of compositions comprising a nucleic acid encoding EC-SOD by local or systemic delivery (e.g. column 6, lines 23-60; column 9, lines 42-51).

Regarding claims 109, 117 and 125, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claims 111, 119 and 127, March teaches the administration of an adenovirus (e.g. column 6, lines 23-60).

Regarding claims 113, 121 and 129, March teaches the treatment of a human (e.g. column 6, lines 40-60).

Claims 50-55, 57-63, 65, 82-87, 89-95, 97-103, 105-111, 113-119, 121-127 and 129 are rejected under 35 U.S.C. 102(e) as being anticipated by Dzau et al (US Patent Application Publication No. 2003/0022870; see the entire reference). This is a new rejection.

Regarding claims 50, 58, 82, 90, 98, 106, 114 and 122, Dzau et al teach a method for treating restenosis in a mammal, comprising administering to the mammal a composition comprising a nucleic acid encoding extracellular superoxide dismutase in a therapeutic amount such as $10^7$-$10^{13}$ viral particles (e.g. paragraphs [0007]-[0012] and [0073]). The composition comprising the nucleic acid is a composition comprising an isolated nucleic acid or a composition comprising a cell comprising the nucleic acid (e.g. paragraphs [0072]-[0081]). Absent any evidence to the contrary, the nucleic acid encoding EC-SOD is delivered at an amount sufficient to reduce blood vessel thickening, reduce macrophage accumulation, and increase endothelial cell growth.

Regarding claims 51, 59, 83, 91, 99, 107, 115 and 123, Dzau et al teach local delivery of the nucleic acid composition (e.g. paragraphs [0071] and [0074]-[0076]).

Regarding claims 52, 60, 84, 92, 100, 108, 116 and 124, Dzau et al teach the delivery of naked nucleic acid (e.g. paragraphs [0068] and [0071]).

Regarding claims 53, 61, 85, 93, 101, 109, 117 and 125, Dzau et al teach the delivery of the nucleic acid in the form of a virus such as an adeno-associated virus (e.g. paragraph [0068]).

Regarding claim 54, 62, 86, 94, 102, 110, 118 and 126, Dzau et al teach the delivery of the naked DNA in the form of a liposome (e.g. paragraph [0071]).

Regarding claims 55, 63, 87, 95, 103, 111, 119 and 127 Dzau et al teach the delivery of the naked DNA or nucleic acid encoding EC-SOD in the form of a biocompatible polymer matrix such as a hydrogel (e.g. paragraphs [0075]-[0076]).

Regarding claim 57, 65, 89, 97, 105, 113, 121 and 129, Dzau et al teach the delivery of the nucleic acid to a human (e.g. paragraph [0067]).

Claims 66, 67, 72-75, 80, 81, 98, 99, 104-107, 112-115, 120-123, 128 and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Marklund et al (US Patent No. 5,366,729, of record; see the entire reference) as evidence by Syuryapranata et al (Circulation, Vol. 97, pages 2502-2505, 1998). This is a new rejection.

Regarding claims 66, 74, 98, 106, 114 and 122, Marklund et al teach the administration of a pharmaceutical composition comprising a polypeptide having superoxide dismutating property of native EC-SOD in a therapeutically effective dose (e.g. column 31, lines 25-68). Further, Marklund et al claim a method for preventing or treating a disorder at least in part caused by or exacerbated by the presence or formation of superoxide radicals, wherein the disorder is damage caused by ischemia followed by reperfusion, or in connection with the

transplantation of organs selected from the group consisting of kidney, lung, pancreas, liver, skin, bone tissue, extremities, skeletal muscle, lens, and cornea, or in connection with heart surgery, comprising administering a therapeutically or prophylactically effective amount of a polypeptide or a polypeptide composition comprising a non-naturally occurring EC-SOD-like polypeptide of claim 1 before, during or after surgery (claims 1 and 14).

Regarding claims 67, 75, 99, 107, 115 and 123, Marklund et al teach the systemic administration of the EC-SOD protein (e.g. column 31, lines 35-68).

Regarding claims 72, 80, 104, 112, 120 and 128, Marklund et al teach repeated administration of the EC-SOD protein at a dosage of about 15-600 mg/day (e.g. column 31, lines 35-68).

Regarding claims 73, 81, 105, 113, 121 and 129, Marklund et al teach the treatment of a human with EC-SOD polypeptide (e.g. column 31, lines 35-68).

The claims read on the teachings of Marklund et al because Marklund et al teach the claimed method step of administering an EC-SOD polypeptide. The patient population that Marklund et al teach is individuals that have a myocardial infarction (e.g. columns 25-26). Stenting and balloon angioplasty are routine treatments of patients with myocardial infarction (Syuryapranata et al. Circulation, Vol. 97, pages 2502-2505, 1998). Thus, an individual with myocardial infarction is likely to be treated with stenting or balloon angioplasty and will be at risk of restenosis. Marklund et al teach the use of a therapeutically effective dose to treat myocardial infarction or ischemia/reperfusion injury. Therefore, absent any evidence to the contrary, administration of EC-SOD protein to subjects with myocardial infarction will necessarily reduce the pathology typically associated with restenosis.

Claims 50-53, 57-61, 65-59, 73-77, 81-85, 89-92, 97-101, 105-108, 113-117, 121-125 and 129 are rejected under 35 U.S.C. 102(e) as being anticipated by French (US Patent Application Publication No. 2002/0061299; see the entire reference) as evidenced by Syuryapranata et al (Circulation, Vol. 97, pages 2502-2505, 1998). This is a new rejection.

The claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid encoding an extracellular superoxide dismutase. The amount of the nucleic acid administered must be sufficient to treat and/or prevent restenosis, treat and/or prevent blood vessel thickening, decrease macrophage accumulation, increase endothelial cell growth, or inhibit hyperplastic connective tissue growth.

Regarding claims 50, 58, 66, 74, 82, 90, 98, 106, 114 and 122, French teaches the administration of a recombinant adenovirus (Ad5) gene therapy vector comprising a nucleic acid sequence encoding extracellular superoxide dismutase (EC-SOD) to a mammal to treat ischemia/reperfusion injury such as myocardial infarction (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045]). Further, French teaches a sufficient quantity of gene therapy vector to achieve systemic elevations in EC-SOD therapeutic protein (e.g. paragraph [0008]).

Regarding claims 51, 59, 67, 75, 83, 91, 99, 107, 115 and 123, French teaches the administration of the adenoviral vector comprising a nucleic acid encoding EC-SOD by systemic or local delivery (e.g. paragraph [0008]).

Regarding claims 52, 60, 68, 76, 84, 92, 100, 108, 116 and 124, French teaches the administration of the nucleic acid encoding EC-SOD in plasmid (i.e. naked) form (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045], claims 1, 2 and 5).

Regarding claims 53, 61, 69, 77, 85, 93, 101, 109, 117 and 125, French teaches the delivery of the EC-SOD nucleic acid in an adenoviral vector or an adeno-associated virus (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045], claims 1-4).

Regarding claims 57, 65, 73, 81, 89, 97, 105, 113, 121 and 129, French demonstrates the utility of the gene therapy method in a rabbit model (e.g. paragraphs [0021]-[0028]). French teaches that the rabbit model closely mimics the human condition of a heart attack (e.g. paragraph [0006]). Further, French et al teach the use of the human cDNA encoding EC-SOD (e.g. paragraph [0024]). Moreover, French envision the treatment of any patient (e.g. claim 1). Thus, French teaches the administration of a nucleic acid encoding EC-SOD to a human patient.

The claims read on the teachings of French because French teaches the claimed method step of administering a nucleic acid encoding an extracellular superoxide dismutase. The patient population that French teaches is individuals that have or could potentially have a myocardial infarction (e.g. Abstract; paragraph [0008]). Stenting and balloon angioplasty are routine treatments of patients with myocardial infarction (Syuryapranata et al. Circulation, Vol. 97, pages 2502-2505, 1998). Thus, an individual with myocardial infarction is likely to be treated with stenting or balloon angioplasty and will be at risk of restenosis. As disclosed in the instant specification, an adenoviral vector comprising a nucleic acid encoding EC-SOD administered at a dosage of $3x10^9$ pfu/kg is sufficient to induce a therapeutic effect. This dosage is similar to the dosage of $2x10^8$ pfu/kg taught by French. Further, French teaches that the dosage used was

capable of increasing SOD activity in the heart 5.4-fold. Therefore, absent any evidence to the contrary, administration of EC-SOD protein to subjects with myocardial infarction will necessarily reduce the pathology typically associated with restenosis.

***Response to Arguments - 35 USC § 102***

With respect to the rejection of claims 66, 67, 72-75, 80, 81, 98, 99, 104-107, 112-115, 120-123, 128 and 129 under 35 U.S.C. 102(b) as being anticipated by Marklund et al, Applicant's arguments filed 4/10/2006 have been fully considered but they are not persuasive.

The response asserts that Marklund does not provide their own evidence, but relies on the prior art. Further, the response appears to assert that the prior art relied upon by Marklund is related only to SOD1 or SOD2 and not to SOD3 (EC-SOD). This is not found persuasive because a patent specification may rely upon the teachings of the prior art. Furthermore, the teachings of the prior art specifically relied upon by Marklund et al are directed to EC-SOD (e.g. column 31, lines 6-34).

The response asserts that Marklund does not test the EC-SOD protein in a disease model. Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. In the instant case, Marklund relies on the prior art for an enabling disclosure (e.g. column 31).

With respect to the comments directed to the difference between myocardial ischemia and restenosis, the difference between the medical condition of myocardial ischemia and the medial treatment of restenosis is acknowledged. However, stenting and balloon angioplasty are routine treatments of patients with myocardial infarction (Syuryapranata et al. Circulation, Vol.

97, pages 2502-2505, 1998). Thus, an individual with myocardial infarction is likely to be treated with stenting or balloon angioplasty and will be at risk of restenosis. Accordingly, administration of EC-SOD protein to subjects with myocardial infarction will necessarily reduce the pathology normally associated with restenosis.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 50-53, 57-61, 65-59, 73-77, 81-85, 89-92, 97-101, 105-108, 113-117, 121-125 and 129 under 35 U.S.C. 102(e) as being anticipated by French (US Patent Application Publication No. 2002/0061299), Applicant's arguments filed 4/10/2006 have been fully considered but they are not persuasive.

The response asserts that restenosis is not disclosed by French. This is not found persuasive because French teaches the administration of gene therapy to protect the intact mammalian heart against myocardial infarction. Stenting and balloon angioplasty are routine treatments of patients with myocardial infarction (Syuryapranata et al. Circulation, Vol. 97, pages 2502-2505, 1998). Thus, an individual who is protected from myocardial infarction will also be protected from restenosis and the typical pathology associated with restenosis.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56, 64, 88, 96, 104, 112, 120 and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laukkanen et al (Circulation, Vol. 106, pages 1999-2003, September 16, 2002; see the entire reference).

The teachings of Laukkanen et al are described above and applied as before.

Laukkanen et al do not teach repeating the step of administering the composition comprising the adenovirus encoding EC-SOD.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Laukkanen et al to include the administration of the adenovirus a second time because Laukkanen et al teach it is within the ordinary skill in the art to use the adenovirus expressing EC-SOD to reduce the pathological effects of restenosis.

One would have been motivated to make such a modification in order to receive the expected benefit of further reducing the pathological effects of restenosis. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### *Response to Arguments*

Applicant's arguments with respect to claims 50-129 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection. The previous rejection of claims 50-129 has been withdrawn.

### *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER